REMARKS

Pursuant to the Examiner's suggestion, Applicants have amended claims 1, 4, 5, and 11-14 to particularly point out and distinctly claim the subject matter which they regard as their invention. In particular, claims 1 and 12 have been amended to recite "desired" instead of "heterologous," support for which can be found in the Specification, page 5, line 18. Supports for the correction can be found in the Specification, page 4, lines 21-22. No new matter has been added.

Claims 1-14 are currently pending. Reconsideration of this application, as amended, is respectfully requested in view of the remarks below.

Objections

The Examiner objects to Figures 5A-6G and Figures 7A-7B for certain deficiencies. See the Office Action, page 2. Applicants will rectify these deficiencies after this application has been allowed.

The Examiner also objects to the term "ATCC" recited in claims 9 and 11. Also see the Office Action, page 2. Applicants have replaced the "ATCC" with "American Type Culture Collection."

Double Patenting

As the Examiner correctly points out, SEQ ID NOs: 1 and 2 recited in claims 7 and 8, respectively are identical. Claims 7 and 8, therefore, have identical scope. See the Office Action, page 3, lines 3-6. Indeed, SEQ ID NO:2, depicted in Figures 6A-6G, was repeated as both SEQ ID NOs: 1 and 2 in the original Sequence Listing. As a result, SEQ ID NO:1, depicted in Figures 5A-5G, was omitted from the original Sequence Listing. To overcome this double patenting rejection, Applicants file herewith a substitute Sequence Listing containing revised SEQ ID NO:1.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1, 4, 5, and 11-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. See the Office Action, pages 11-13.

Applicants submit that this rejection has been overcome by the above amendments.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1, 9, 11, and 13 under 35 U.S.C. § 112, first paragraph, on three different grounds. See the Office Action, pages 3-10. Applicants respectably traverse each ground as follows:

I

The Examiner rejects claims 9 and 11 on the ground that "claims 9 and 11 refer to biological deposits to satisfy the 'how to make' requirement, but fail to specify if they were made under the terms of the Budapest Treaty" (the Office Action, page 3, lines 13-15).

According to the Examiner, this deficiency may be rectified by a statement "stating that the specific plasmids and the bacterial strain have been deposited under the Budapest Treaty and without restriction released to the public upon the issuance of a patent." See the Office Action, page 3, lines 18-21. Applicants file herewith a Declaration of Availability containing such a statement.

II

The Examiner rejects claim 1 on the ground that "[t]he Specification does not teach how to make and use the invention with any and all [desired] genes." See the Office Action, page 6, lines 9-11.

Admittedly, the Specification does not provide guidance as to how to insert any and all desired genes into an expression cassette and express them in cells. However, it does teach how to insert a gene (e.g., β-galactosidase gene) into a vector. See Figures 1-4. This teaching is applicable to the insertion of a desired gene into an expression cassette. Indeed, it is merely a routine to insert a gene of one's own choice into an expression cassette and express it. For example, Manoharan *et al.* (1997, *Gene* 193: 229-237) teaches inserting cyclin A into a vector pGFLEC and expressing a GST-fused cyclin A protein in *E. coli*. See Exhibit A attached hereto.

Greenberg *et al.* (1994, *Mol. Endo.* 8: 230-239) teaches inserting the bacterial chloramphenicol acetyltransferase gene into a rat probasin-containing vector and expressing the bacterial chloramphenicol acetyltransferase transgene in murine prostate cells. See Exhibit B attached hereto. Further, Yew *et al.* (1997, *Human Gene Therapy* 8: 575-584) teaches inserting human placental alkaline phosphatase gene to a CMV-containing plasmid and expressing it in murine lung cells. See Exhibit C attached hereto. Note that all of the just-described articles were published before this application was filed.

It is well established that not every detail as to how to practice a claimed invention need to be disclosed in the specification. In fact, "[a] patent need not teach, and **preferably omits**, what is well known in the art." See the Manual of Patent Examining Procedure (MPEP), § 2164.01; emphasis added. All that is necessary is that one skilled person in the art be able to practice the claimed invention. As described above, an artisan would be able to insert a gene into an expression cassette and express it without any guidance. Thus, the Specification need not teach, and preferably omits, how to make a Lac shuttle vector containing an expression cassette into which a desired gene is inserted.

The Examiner also asserts that "[t]he Specification does not teach how to make and use the invention ... with any and all non-antibiotic resistance genes as marker genes under the control of any and all promoters as claimed." See the Office Action, page 6, lines 9-12.

The Specification teaches use of a β-galactosidase gene as a non-antibiotic resistance marker gene under the control of erythromycin resistance gene promoter. See pages 8-9 and 12-20. Without the teachings in the Specification, a skilled person in the art would also know how to make and use a non-antibiotic resistance marker gene and its control promoter at the time this application was filed. For example, Sorensen *et al.* (2000, *Applied and Environmental Microbiology* 66: 1253-1258) teaches using *Sup D* as a non-antibiotic resistance gene marker, which is under the control of *Sup D* promoter . See Exhibit D attached hereto. Platteeuw *et al.* (1996, *Applied and Environmental Microbiology* 62: 1008-1013) discloses a non-antibiotic resistance gene marker, *lacF*, under the control of Rep C promoter. See Exhibit E attached hereto. Dickely *et al.* (1995, *Molecular Microbiology* 15: 839-847) discloses a non-antibiotic

resistance gene marker, *Sup B*, under the control of a tRNA promoter. See Exhibit F attached hereto.

Not only has the Specification enabled a skilled person in the art to make the Lac shuttle vector of claim 1, it has also provided guidance on how to use such a Lac shuttle vector. For example, a Lac shuttle vector containing an antigenic gene is induced into *Lactobacillus casei* cells by transformation, followed by administration to a subject. See the Specification, page 10, lines 11-20.

The Examiner relies on the Forman factors to support this non-enablement rejection. See the Office Action, page 5, lines 12-17. Applicants have considered all of the factors, and submit that, for the reasons set forth above, one skilled in the art would be enabled to make and use a Lac shuttle vector of claim 1 without undue experimentation.

III

The Examiner rejects claim 13 on the ground that "[t]he Specification does not provide an enabling disclosure for the treatment or prevention of any and all diseases by administering the said Lac vector." See the Office Action, page 8, lines 3-4. Amended claim 13 is drawn to a DNA vaccine composition containing a Lac shuttle vector of this invention.

To support this rejection, the Examiner cites as many as six references, and asserts that "[a]t the time of filing the art recognized that while many immunization strategies using specific antigens were capable of generating an immune response against the particular antigen, few were capable of generating protective or therapeutically effective immune response against infections or diseases associated with the immunizing antigen." See the Office Action, pages 7-10.

The Examiner appears to reject claim 13 on lack of an asserted utility, rather than on lack of teachings of how use the claimed composition. Applicants believe that the Examiner should have imposed a separate rejection under 35 U.S.C. § 101. See the MPEP, § 2164.07 I(A).

In any event, Applicants would like to bring to the Examiner's attention a statement in the MPEP § 2107.02III, "[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using ***in vitro*** assays, **or** from testing in an animal model **or** a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process" (emphases added). Thus, if

reasonably correlated to an asserted particular utility, ***in vitro* data alone is sufficient**. Yet, Applicants have obtained ***in vivo* data** to support the utility of claim 13.

Applicants submit herewith a Declaration of Dr. Wei-Yu Lo under 37 C.F.R. § 1.132. Dr. Lo's Declaration provides experimental data showing that immunization of mice with an AFP-expression Lac shuttle vector (pCLP7/AFP)-transduced cells generated far more potent AFP-specific immune response, as compared with a control. It has been established that immune response induced by AFP resulted in *in vivo* protection against AFP-producing murine tumors. See Vollmer *et al.* (1999) *Cancer Research* 59: 3064-3067, a copy of which is attached hereto as Exhibit G.

For the reasons set forth above, Applicants request the Examiner withdraw the rejection of claim 13.

Rejection under 35 U.S.C. § 103

Claims 1-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bringel *et al.* (1989, *Plasmid* 22:193-202), in view of Hemme *et al.* (1994, *Letters in Applied Microbiology* 19: 345-348) and Dietrich *et al.* (1998, *Nature Biotechnology* 16: 181-185).

Amended claim 1, the only independent claim, will be first discussed.

Claim 1 is drawn to a Lac shuttle vector that includes four elements: (a) a region containing an *E. coli* replication origin sequence; (b) a eukaryotic gene expression cassette, wherein a desired gene is inserted; (c) a lactic acid bacteria plasmid sequence; and (d) a marker gene that is not an antibiotic resistance gene under the control of a promoter sequence thereof.

The primary reference Bringel *et al.* discloses a construct containing a sequence of an *E. coli* plasmid (i.e., pUC19); a sequence of a *Lactobacillus plantarum* plasmid (i.e., pLP1); and a sequence of an erythromycin-resistance gene. See Fig.1. Bringel *et al.* is totally silent on element (b) recited in claim 1 (i.e., a eukaryotic gene expression cassette) and on element (d) recited in claim 1 (i.e., a non-antibiotic resistance marker gene under the control of a promoter).

Dietrich *et al.* teaches element (b). More specifically, it describes a eukaryotic expression cassette containing an antigen gene. Hemme *et al.*, on the other hand, teaches

element (d). More specifically, it describes a non-antibiotic resistance marker gene, i.e., β-galactosidase gene, apparently under the control of a promoter.

According to the Examiner, "[m]otivation to combine the teachings ... was provided by the state of the art at the time of filing and the need to address the safety issues in DNA vaccination (see Dietrich *et al.* , page 184, right column, 2nd paragraph)." The Examiner proceeds to conclude that " it would have been obvious to a person with ordinary skill in the art to combine the teachings of Bringel *et al.*, Hemme *et al.*, and Dietrich *et al.* and arrive at the Lac shuttle vector of the instance invention." See the Office Action page 14, lines 12-18.

Applicants disagree. Admittedly, Dietrich *et al.* and Hemme *et al.*, respectively, teach elements (b) and (d), both of which are missing from Bringel *et al.* However, none of Bringel *et al.*, Hemme *et al.*, and Dietrich *et al.* suggests combining the teachings in the three references to arrive at the Lac shuttle vector of claim 1. As a matter of fact, Bringel *et al.* **teaches away** from the combination.

More specifically, Bringel *et al.* states:

> "inserting 4.5-kb DNA [i.e., an *E. coli* plasmid, (pUC19) and an erythromycin-resistance gene taken from the plasmid pVA891] in the pLP1 plasmid **decreased considerably** its segregational stability even if the pLP1 plasmid is very stable in *L. plantarum* CCM 1904 (all the attempts to cure pLP1 with different chemicals failed). The pULP-type vectors [containing pLP1 and an *E. coli* plasmid, i.e., pUC19] are lost in *L. plantarum* after 20 generations without selective pressure, **strongly limiting** their use as a gene transfer tool in industrial strains which are grown on complex media" (emphases added). See page 200, left column, line 10 to page 201, right column, line 2.

Clearly, Bringel *et al.* suggests **not combining** a lactic acid bacteria plasmid sequence with a region containing an *E. coli* replication origin sequence and an antibiotic (or non-antibiotic) resistance gene, let alone with an additional eukaryotic gene expression cassette. Thus, it is improper to combine the three references.

For the reasons set forth above, claim 1 is non-obvious in view of Bringel *et al.*, Hemme *et al.*, and Dietrich *et al.* So are claims 2-14, all of which depend from claim 1.

CONCLUSION

For the reasons set forth above, Applicants submit that the grounds for the rejections asserted by the Examiner have been overcome, and that the claims, as pending, define subject matter that is novel and nonobvious over the prior art.

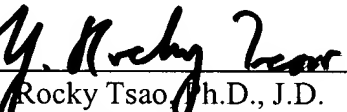
Attached is a marked-up version of the changes being made by the current amendment.

Applicants submit that all of the claims are now in condition for allowance, which action is requested. Pursuant to 37 CFR § 1.136, applicant hereby petitions that the period for response to the action dated November 27, 2001, be extended for two months to and including April 27, 2002. Enclosed is a check for $200 for the required fee.

Please apply any other charges to Deposit Account No. 06-1050, referencing 12875-002001.

Respectfully submitted,

Date: 4-22-02



Y. Rocky Tsao, Ph.D., J.D.
Attorney for Applicants
Reg. No. 34,053

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Replace the original Sequence Listing with the substitute Sequence Listing filed herewith.

In the claims:

Claims 1, 4, 5, 9, and 11-14 have been amended as follows:

Claim 1. (Amended) A Lac shuttle vector, comprising:

(a) a region which regulates a plasmid copy number, wherein said region comprises an E.coli replication origin sequence;

(b) [an] a eukaryotic gene expression cassette, which comprises [an] a eukaryotic gene [site and a] transcriptional [terminator sequence,] promoter sequence, a multiple cloning site and a transcriptional terminator sequence, wherein a [heterologous] desired gene is inserted into said multiple cloning site;

(c) a lactic acid bacteria plasmid sequence, which comprises a plus origin of replication, and a nucleic acid sequence encoding [for] a protein which [relates to] is involved in replication of the lactic acid bacteria plasmid; and

(d) a [non-antibiotic resistance selection gene] marker gene that is not an antibiotic resistance gene and the promoter sequence thereof.

Claim 4. (Amended) The Lac shuttle vector as claimed in claim 3, wherein the protein which [relates to] is involved in the lactic acid bacteria plasmid replication is Rep A protein [containing] consisting essentially of 317 amino acids.

Claim 5. (Amended) The Lac shuttle vector as claimed in claim 1, wherein said [non-antibiotic resistance selection] marker gene is β-galactosidase gene.

Claim 9. (Amended) The Lac shuttle vector as claimed in claim 1, wherein the Lac shuttle vector is selected from the group consisting of:

(a) pCLP7 [(]having the configuration of restriction sites in FIG. [3] 4, [ATCC] American Type Culture Collection Accession No. PTA-2661[)]; and

(b) pCLP8 [(]having the configuration of restriction sites in FIG. [3] 4, [ATCC] American Type Culture Collection Accession No. PTA-2663[)].

Claim 11. (Amended) The Lac shuttle vector as claimed in [anyone of] claim 10, wherein the host cell is the Lac- mutant of *Lactobacillus casei*, [(]subsp. Casei[)], which is designated Ana-1 [(Lac- mutant)], [(ATCC] American Type Culture Collection Accession No. PTA-2662[)].

Claim 12. (Amended) A kit for expression of a [heterologous] desired gene, comprising:

(a) the Lac shuttle vector as claimed in claim 1;

(b) a host cell which the endogenous β-galactosidase gene thereof is not capable of producing a normal enzymatic function; and

(c) an eukaryotic cell.

Claim 13. (Amended) A DNA vaccine [carrier] composition comprising the Lac shuttle vector as claimed in claim 1.

Claim 14. (Amended) A method for selection of a host cell containing a vector, comprising:

(i) introducing into said host cell the Lac shuttle vector as claimed in claim 1,

wherein the endogenous β-galactosidase gene of said host cell is not capable of producing a normal enzymatic function; and

(ii) culturing said host cell transformed in step (i) under conditions which lactose is the only carbon source,

thereby selecting a host cell comprising Lac shuttle vector of claim 1.